EXHIBIT 3

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Individualizing hypertension treatment with impedance cardiography: a meta-analysis of published trials

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***Abstract*:**

Objective: Hypertension affects 73 million Americans and costs the US healthcare system over $73 billion annually. Despite increasing awareness of the consequences of uncontrolled hypertension, numerous antihypertensive pharmacologic clinical studies and consistent updates to hypertension guidelines, control rates are suboptimal and have not met national goals. Among treated hypertensives, only 45% of women and 51% of men have reached blood pressure (BP) levels below 140/90 mmHg. Individualization of antihypertensive regimens with hemodynamic information from impedance cardiography (ICG) has been advocated to further improve hypertension control rates. We therefore undertook a quantitative analysis of the trials evaluating the role of ICG as an adjunct to therapeutic decision-making in the treatment of hypertension and the attainment of BP control.

Methods: Five studies comprising a total population of 759 patients met the inclusion criteria. Two randomized controlled trials (RCTs) involving a total of 268 patients and three single-arm prospective trials with 491 patients were evaluated using ICG data to guide therapeutic decision-making in the treatment of hypertensive patients.

Results: Significant benefit was found in both RCTs for ICG-guided BP treatment. The combined odds ratio for the two trials was 2.41 (95% CI = 1.44–4.05, $p = 0.0008$), in favor of ICG treatment, meaning that it was more than twice as likely to achieve BP success when using ICG than if ICG was not used. Success attainment of goal BP of <140/90 mmHg was 67% in the ICG-guided arms of the combined randomized trials. Overall success in the single-arm prospective trials of ICG-guided BP treatment was a similar 68%.

Conclusion: The results of this meta-analysis confirm the value of using ICG-derived hemodynamic data as an adjunct to therapeutic decision-making in the treatment of hypertension. The data reviewed here demonstrate that ICG-based approaches are in keeping with previously advocated strategies incorporating patient-individualized drug regimens, evidence-based medicine, and practical, easy to apply, cost-effective principles to further improve hypertension control rates.

***Keywords*:** hypertension, hemodynamics, impedance cardiography, medical management therapy

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Introduction

Hypertension has significant public health, clinical, and economic consequences for the health care system and our society [Stason, 2009]. It is a complex, hemodynamic disorder affecting approximately 73 million Americans [Members, 2009] and costs the US healthcare system over $73 billion annually [Stason, 2009]. Accordingly, in the US, hypertension is the most common primary diagnosis code for ambulatory clinical visits. It is a major, modifiable risk for potentially debilitating cardiovascular (CV) conditions such as heart failure and stroke, chronic kidney disease (CKD) and coronary heart disease [Chobanian *et al.* 2003]. Epidemiological studies have shown that

cardiovascular disease (CVD) risk begins to rise at a blood pressure (BP) level that is well within the normal range (~115/75 mmHg) and that CVD risk doubles for each 20/10 mmHg increasing increment in BP [Izzo *et al.* 2008]. Hypertension has been estimated to account for 50% of potentially reversible heart disease and 75% of stroke risk worldwide [Members, 2009]. Reduction of BP by 5–6 mmHg can decrease the risk of stroke by 40%, and reduces the likelihood of dementia, heart failure, and mortality from CVD [Lewington *et al.* 2002].

Among all hypertensives, BP control rates have improved over time rising from 10% in the 1970s to 45% in 2009 [Members, 2009]. Among hypertensive patients receiving pharmacotherapy, BP control rates have progressed from 31% to approximately 45% in women and 51% in men [Gu *et al.* 2008]. While encouraging, hypertension control rates are suboptimal and have fallen short of national goals, including the US Department of Health and Human Services (DHHS) 'Healthy People 2010' program targeting a 50% control rate for all hypertensive patients and 70% for those treated by 2010 [Services, 2000].

In drug-treated hypertensives, multiple factors contribute to poor BP control, including patient non-compliance with prescribed medications, therapeutic inertia, and prescription of suboptimal drug regimens (e.g. inadequate dosing of drugs, too few drugs, ineffective drug combinations, absence of diuretics in complex drug regimens) [Yakovlevitch and Black, 1991]. Also the presence of associated risk factors have been shown to contribute to resistance in the BP lowering effect of antihypertensive agents. These include obesity, albuminuria/proteinuria, presence of pressure-related target-organ injury, reduced kidney function, insulin resistance and advanced age [Cushman *et al.* 2008; Nasser *et al.* 2008; Lloyd-Jones *et al.* 2000].

High BP results from one or more hemodynamic derangements, including elevated cardiac output (CO)/cardiac index (CI), systemic vascular resistance (SVR)/systemic vascular resistance index (SVRI), and blood volume. Clinical and health policy experts have emphasized that tailoring antihypertensive medicines to patients' underlying pathophysiologic/hemodynamic conditions are important considerations for the future treatment of hypertension [Stason, 2009; Smith and Levy, 2008; Ferrario *et al.* 2007; Flack, 2006; Smith *et al.* 2006; Taler *et al.* 2002]. Although the practice of personalized medicine has been elusive in many areas of medicine, including hypertension, and is often thought of in terms of genetic traits, there are *individual* phenotypic characteristics amenable to measurement in specific clinical settings, such as noninvasively-measured hemodynamic parameters, that have been shown, at least over the short term (~3 months), to improve BP responses and BP control rates when used to guide the selection of antihypertensive drug therapy [Aoka, 2009; Sramek *et al.* 2008; Smith *et al.* 2006; Taler *et al.* 2002]. Noninvasive hemodynamic data allow identification of traits unique to the *individual* that accurately predict therapeutic responses and/or toxicities to pharmacological or other interventions.

Impedance cardiography (ICG) [Ferrario *et al.* 2007] is a noninvasive, low-cost technology which easily measures a patient's hemodynamic phenotypic profile. ICG data allows tailoring specific antihypertensive therapeutic choices to an *individual's* hemodynamic profile thereby maximizing the BP lowering response for the given therapeutic selection. ICG has been used in both primary care as well as hypertension specialty settings to improve rates of BP control relative to usual physician therapeutic decision-making in these settings. This study, a meta-analysis of published studies involving use of ICG-guided therapy in attainment of BP control in hypertensive patients, evaluated the impact of adjunctive use of ICG data by the treating physician in therapeutic decisions designed to achieve BP goal.

Methods

Impedance cardiography technology

ICG uses four sets of dual sensors placed laterally on the neck and on the chest at the mid-axillary location (Figure 1). Four of the sensors transmit low-amplitude, high-frequency alternating electrical current that is not perceived by the patient while the other four sensors measure changes in electrical impedance as a result of changes in the thoracic cavity. The changes in blood volume in the aorta, with changes in the cardiac cycle, result in changes in electrical conductivity and therefore thoracic impedance. The baseline and cardiac cycle changes in thoracic impedance are used to calculate hemodynamic parameters (Figure 1). The ICG test takes approximately ten minutes

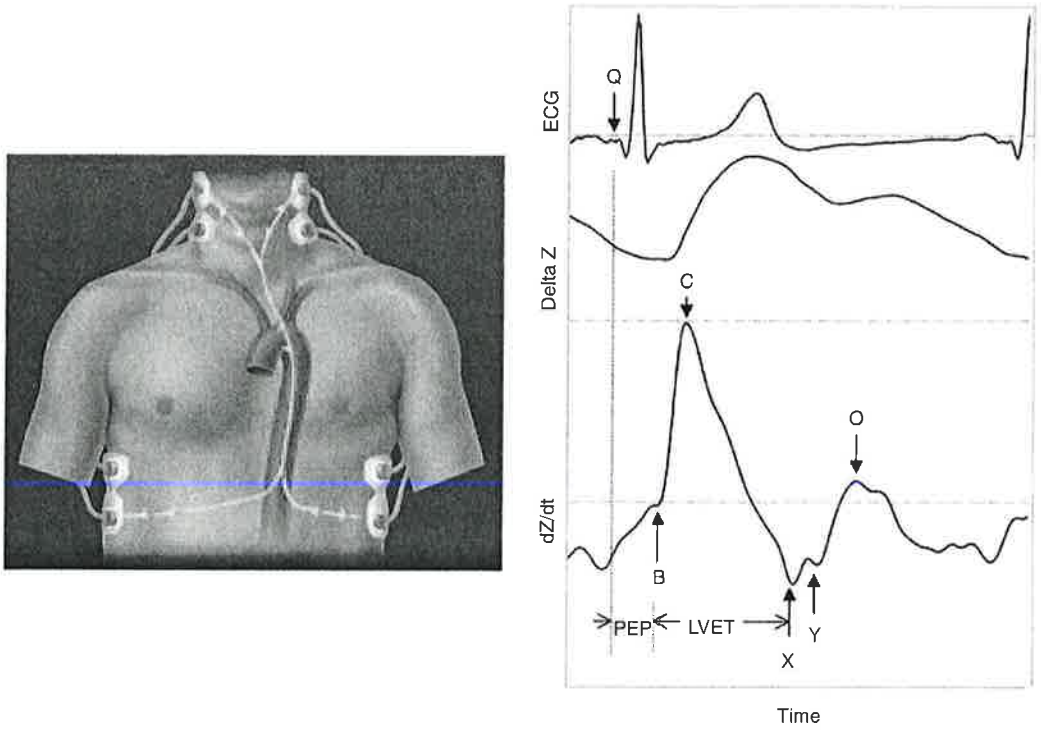


Figure 1. Impedance cardiography (ICG) method showing the application of dual sensors on the neck and chest (left) and ECG and two ICG waveforms from which fiducial points are derived (right). LVET, left ventricular ejection time; PEP, pre-ejection period.

to perform, including application of the electrodes, entering required patient information, and obtaining a complete patient hemodynamic profile in an ICG status report. Key measurements of CO, CI, stroke volume ratio (SVr), SVRI, and thoracic fluid content (TFC) are among the multiple hemodynamic parameters provided. The devices have received FDA 510(k) clearance, and accuracy and reproducibility of these measurements have been validated and published elsewhere [Treister *et al.* 2005; Albert *et al.* 2004; Van De Water *et al.* 2003; Sageman *et al.* 2002; Drazner *et al.* 2002].

Treatment algorithms for ICG-guided antihypertensive therapy selection have followed similar principles as depicted in Figure 2. Specifically, an elevated cardiac output/index would recommend the selection or uptitration of a beta blocker or nondihydropyridine calcium-channel blocker (CCB); an elevated SVr/SVRI would recommend the selection or up titration of an angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB) or dihydropyridine CCB; and an elevated visit-to-visit trending TFC would recommend the selection, uptitration or addition of a diuretic.

Analyzed studies

There have been a number of studies demonstrating the ability of ICG-guided therapy to substantially improve hypertension control rates; therefore, we conducted a meta-analysis of trials using ICG in the treatment of adults with hypertension. Initially, we conducted a literature and reference search in Medline, PubMed, and Cochrane databases as well as the Internet for studies using ICG in the treatment of adults with hypertension. Key words searched were 'hypertension', 'resistant hypertension', 'hemodynamics', 'impedance cardiography', 'therapy individualization' and 'goal-directed therapy'. For inclusion in this review and meta-analysis, studies had to meet two of the following criteria: (1) randomization of adults with a history of mild to resistant essential hypertension and presence of a control group of patients randomly assigned to standard medical care for treatment of their hypertension; (2) nonrandomized, prospective, interventional clinical trial of adults

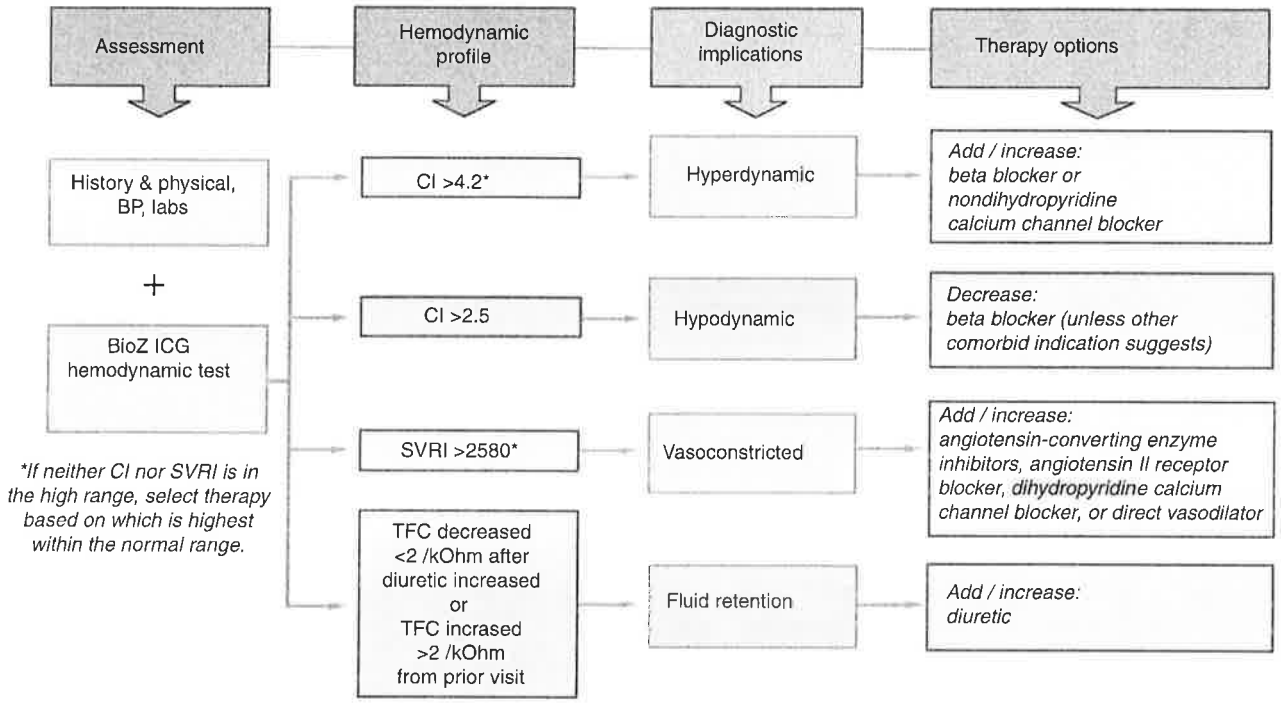


Figure 2. Impedance cardiography-guided algorithm. BP, blood pressure; SVRI, systemic vascular resistance index; TFC, thoracic fluid content, CI, confidence intervals.

demonstrating the impact of ICG-guided therapy on BP control and clinical outcomes; and/or (3) inclusion of detailed reporting of baseline BPs and BPs obtained after a predetermined treatment period using ICG-guided therapy. No studies meeting these criteria were excluded with the exception of women with toxemia in pregnancy. Table 1 summarizes the available studies meeting the inclusion criteria for analysis.

Five studies, based on two study designs and with a total of 759 patients, met the inclusion criteria and were selected for analysis. Two studies were randomized [Smith *et al.* 2006; Taler *et al.* 2002] with a total of 268 patients and three were single-arm, prospective interventional [Aoka, 2009; Sramek *et al.* 2008, 1996] with a total of 491 patients. The two randomized studies were analyzed by first examining their individual odds ratios (OR) in order to determine the improvement in BP control attributable to ICG-guided therapy. The Breslow-Day test was used to determine whether the results across the two studies were sufficiently comparable to justify pooling. The two studies were then combined to perform a pooled analysis of the randomized data to yield an overall OR as depicted in Figure 3. For one randamized controlled trial (RCT) [Smith *et al.* 2006], individual success rates for systolic and diastolic BP were also evaluated and ORs reported. For each of these studies, change in mean systolic and diastolic BP was also summarized and tested for significance across the two treatment arms.

The success rates for the single-arm interventional studies were summarized and compared with a hypothesized outcome that assumed that no intervention took place. The lower one-sided exact confidence boundary of the observed success rate was used to define the maximum rate of becoming normotensive in a hypothetical standard-treatment arm. This lower boundary shows the maximum rate of improvement that could be observed in a standard-treatment arm and still be significantly different from the ICG arm. In order to compare the results from the three single-arm interventional prospective studies with the two randomized trials, those subjects in the two randomized trials assigned to ICG-guided therapy were extracted and their combined rate of success was assessed. Point estimates of success rates and their exact 95th confidence intervals were calculated for the ICG-treated randomized subjects ($n = 119$) as well as for the combined ($n = 491$) Sramek *et al.* [2008, 1996] and the Aoka [2009] subjects.

Table 1. Impedance cardiography in adult hypertension trials.

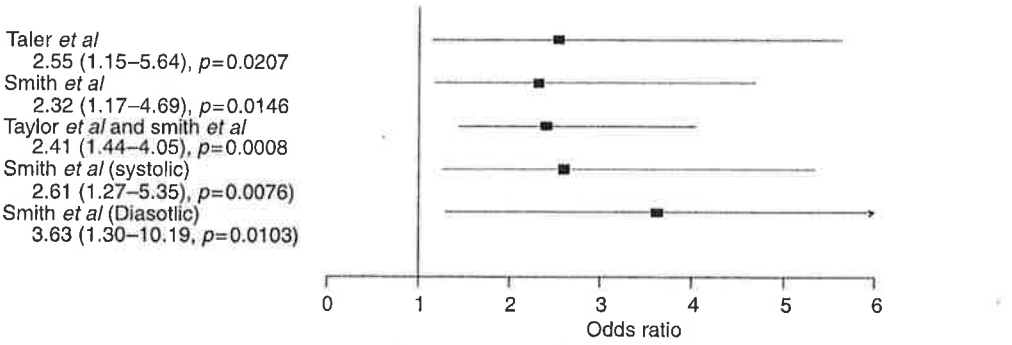
Trial	Author	No. of pts	Design	Trial Duration	Results
Resistant hypertension, 2002	Taler *et al.*	104[1]	Randomized	3 months	OR: 2.55 [1.15–5.64] $p=0.0207$
CONTROL, 2005	Smith *et al.*	164[2]	Randomized	3 months	OR: 2.32 [1.17–4.69] $p=0.0146$; Systolic OR: 2.61 [1.27–5.35] $p=0.0076$; Diastolic OR: 3.63 [1.30–10.19] $p=0.0103$
Combined RCTs resistant HTN and CONTROL		268	Randomized	3 months	OR: 2.41 [1.44–4.05] $p=0.0008$ Combined success rate: 67% [58–76%]
ICG-directed intervention, 1996	Sramek *et al.*	322[1]	Prospective nonrandomized	3 weeks	Success rate: 63% [58–68%]
Treating HTN as a HD disorder, 2006	Sramek *et al.*	56[1]	Prospective nonrandomized	3 months	Success rate: 84% [72–92%]
Limitation of monotherapy and benefit of ICG,[3] 2009	Aoka	113[1]	Prospective nonrandomized	4.7 months	Success rate: 73% [64–81%]
Combined nonrandomized intervention		491	Prospective nonrandomized		Combined success rate: 68% [63–72%]

[1]Single center trial; [2]Multi-center trial; [3]Limitation of monotherapy and benefit of impedance cardiography as a guide for a combination therapy in achieving blood pressure control in essential hypertension. Note: 95% CI is given in parentheses for OR and Success Rates. P-values reflect the probability of the null hypothesis of no association being true.

Results

Taler *et al.* [2002] reported that of the 50 resistant hypertension subjects randomized to ICG-based hypertension management, 28 (56%) achieved BP <140/90 mmHg after 3 months of treatment, compared with 18 of 54 (33%) of those randomized to standard care. There was no significant difference between the control and ICG treatment arms for baseline BP levels, daily doses of medication, CV co-morbidities, contributing causes to hypertension, and target organ damage. At the end of 3 months, however, greater statistically significant reductions in BP were found in the ICG treatment (certified hypertension specialist and ICG) arm than in the standard care (certified hypertension specialist alone) arm. The ICG treatment arm used an established algorithm in the determination of medical therapy based on hemodynamic findings by ICG. The control arm was not limited to choice of antihypertensive medications, doses or combinations of medications [Taler *et al.* 2002]. The OR was 2.55 (95% CI = 1.15–5.64, $p=0.0207$) in favor of ICG treatment, meaning that it was 2.55 times more likely to achieve BP success when using ICG than when ICG was not used. Mean systolic BP dropped from 169 mmHg to 139 mmHg in the ICG arm and from 173 mmHg to 147 mmHg in the standard care arm ($p<0.01$). The decrease in diastolic BP was also greater in the ICG arm with a drop from 87 mmHg to 72 mmHg in the ICG group, compared with a drop from 91 mmHg to 79 mmHg in the standard care group ($p<0.01$).

As with the Taler *et al.* [2002] Resistant Hypertension Mayo Clinic trial, Smith *et al.* [2006] in the Consideration of Noninvasive Hemodynamic Monitoring to Target Reduction of BP Levels (CONTROL) study reported no significant differences between the control and treatment arms for baseline BP levels, patient history, and baseline hemodynamic parameters. At the end of 3 months, there were significantly greater reductions in BP in the ICG treatment (clinician and ICG) arm in comparison to the standard care (clinician alone) arm. The ICG treatment arm based decisions for medical therapy with the use of an established ICG algorithm, similar to the one used by Taler *et al.* [Taler *et al.* 2002]. Treatment in the control arm was not limited by type of antihypertensive medication, doses administered, or combinations of medications prescribed, similar to the Taler *et al.*



Note that the solid square is the odds ratio for the corresponding study labeled on its left; the horizontal lines represent the 95% CI for that odds ratio. any or whose CI does not overlap with an or of 1 indicates a significant association.

Figure 3. Forest plot showing odds ratios with 95% confidence intervals (CI).

[Taler *et al.* 2002] control arm. The Smith *et al.* [2006] CONTROL Study design allowed comparison of BP control between physicians' usual practice care, which consists of published guidelines, usual practice patterns, and/or patient clinical characteristics, and an ICG algorithm directing anti-hypertensive therapy based on hemodynamic data.

Smith *et al.* [2006] reported more than double (55% vs. 27%) control in the ICG treatment arm versus the standard care arm when reviewing a more aggressive BP control of less than 130/85 mmHg. The OR was 3.25 (95% CI: 1.69–6.26, $p=0.0003$) in favor of ICG treatment arm. For a BP <140/90 mmHg, 52 of 69 (77%) randomized to ICG achieved BP control, whereas 54 of 95 (57%) randomized to treatment with standard care achieved that level of BP control after 3 months ($p=.0146$). The OR was 2.32 (95% CI: 1.17–4.69, $p=0.0146$) in favor of ICG treatment arm. Mean systolic BP dropped 19 mmHg in the ICG arm but only 11 mmHg in the standard care arm ($p<0.01$). Similarly, mean diastolic BP dropped by a greater amount in the ICG arm (12 mmHg vs. 5 mmHg, $p<0.001$). Individual systolic and diastolic BP data were available for secondary analysis. For systolic BP, 55 of 69 (80%) achieved a systolic less than 140 mmHg in the ICG arm, but only 57 of 95 (60%) in the standard care arm (OR=2.61, 95% CI: 1.27–5.35, $p=0.0076$). For diastolic BP, 64 of 69 (93%) achieved a diastolic less than 90 mmHg in the ICG arm, and 74 of 95 (78%) in the standard care arm (OR=3.63, 95% CI: 1.30–10.19, $p=0.0103$).

A Breslow-Day test of the homogeneity of the OR across the two randomized studies indicated that the degree of association did not differ significantly ($p=0.8637$). The combined OR estimate from the case-control Manel-Haenszel test was 2.41 (95% CI: 1.44–4.05, $p=0.0008$). The ORs for the two studies separately and pooled, along with their confidence intervals, are illustrated by the Forest plot in Figure 3. The plot shows the point estimate for the OR (indicated by a solid square); the horizontal lines represent the 95% CI for each OR. Any OR whose lower boundary exceeds 1.00, indicates a significant difference between treatment arms, of which all studies depicted exceeded 1.00. An OR greater than 1.0 indicates that ICG is more effective than standard care; an OR of 1.0, indicates no association; and an OR <1.0 would indicate that ICG is less effective than standard care.

The three single-arm interventional studies show that in subjects not previously under hypertensive control and not previously under ICG-guided treatment, a substantial number were able to achieve BP control after ICG-guided hypertension management was initiated. The single-arm 322 patient intervention study conducted by Sramek *et al.* [1996] reported that after a brief three weeks of ICG-based treatment, 203 of 322 (63%) previously hypertensive subjects became normotensive (defined as MAP <105 mmHg). Again, employing a 1-sided exact 95th percent confidence boundary around the observed success rate of 63%, any hypothesized success rate in those not treated with ICG that is lower than 57% would result in the interpretation of a significant benefit to ICG-based treatment.

In a second study of 56 hypertensive patients, conducted by Sramek et al [Sramek *et al.* 2008], 47 (84%) became normotensive after 3 months following ICG-based intervention. The lower one-sided exact confidence boundary around the observed success rate of 84% was 74%. In the study of 113 hypertensives by Aoka [2009], 83 (73%) became normotensive. With a lower one-sided exact boundary of the success rate of 66%, any hypothesized success rate in those not treated with ICG that is lower than 66% would result in the interpretation of a significant benefit to ICG-based treatment. If one would not expect a transition from hypertensive to normotensive in patients treated with standard care to achieve success rates of 57% or 74% as found in the two Sramek *et al.* studies [2008, 1996] or 66% as found in the Aoka study [2009], then we can interpret these intervention studies as providing support that ICG-based hypertension management is more likely to reduce hypertension than is standard care alone.

If we examine only the ICG arms of the two randomized trials, we obtain 80 successes in 119 subjects treated with ICG. This yields a success rate of 67% with a (CI = 0.58–0.76). From the two single-arm interventional trials by Sramek *et al.* [2008, 1996] or the Aoka trial [2009], we are not able to calculate an OR, as we do not have a control arm in either study. We can examine the obtained success rate to see how closely it corresponds to the success rate in similarly treated subjects from the randomized trials. The three single-arm interventional studies yield information on 491 subjects, 333 of whom achieved normotensive status after ICG-directed intervention. This combined success rate of 68% (CI = 0.63–0.72) is remarkably close to the 67% found in the active arms of the randomized trials.

Discussion

The use of ICG hemodynamic information to guide therapy and thus improve control rates of hypertension was clearly demonstrated in this meta-analysis of two prospective, randomized trials and three prospective, single-arm interventional trials. The OR for the trials of Taler *et al.* [2002] and Smith *et al.* [2006] were 2.55 and 2.32, respectively. The combined ORs for the two studies was 2.41 in favor of ICG-guided treatment, indicating that it was more than twice as likely to achieve BP success when using ICG than when ICG was not used. When the ICG-guided arms of the two randomized trials were compared to the three single-arm interventional trials of Sramek *et al.* [2008, 1996] and Aoka [2009], comparable BP success rates of 63%, 84% and 73%, respectively, were found.

The presumed mechanism for improved BP control with ICG-guided intervention is primarily due to individualized antihypertensive drug selection targeted at the hemodynamic cause of elevated BP. ICG treatment algorithms incorporate noninvasive hemodynamic measurements, as described in the Methods section of CO, CI, SVr, SVRI, and TFC; specifically, these parameters provide data on the underlying cause of elevated BP and can guide the clinician to select and tailor appropriate antihypertensive therapy to the patients' hemodynamic pathophysiologic conditions. The degree to which elevated BP can be related to increase in SVr with or without increases in CO and TFC can indicate the relative need for the vasodilating effects of renin–angiotensin system (RAS) blockade with ACEIs, ARBs, dihydropyridine CCBs or direct vasodilators; the sympatholytic effects of sympathetic nervous system (SNS) blockade with beta blockers; and the reduction of blood volume with diuretics, respectively, in a given patient.

Despite the fact that multiple factors have been identified as important mechanisms related to the development and maintenance of elevated BP, the activation of the RAS, the SNS, and the adrenal–mineralocorticoid axis have been shown to play a central role in creating the various hemodynamic phenotypes (high vascular resistance, increased cardiac output and increased fluid volume). These neurohormonal systems are all generally active in the hypertensive patient, but in a given individual there may be variations in the degree to which one or more systems are active. Clinically, it is not easy to determine which system is dominating the hemodynamic expression of a patient's hypertension, but accurate measurement and analysis of the underlying hemodynamic profile, with ICG, gives significant insight into the varying degrees of activation.

Other ICG-related components may contribute to improved BP control rates. Specifically, the ICG status report (as depicted in Figure 4) indicates whether parameters are low, normal or high, and also provides visit-to-visit parameter changes. The report has served as a tool for

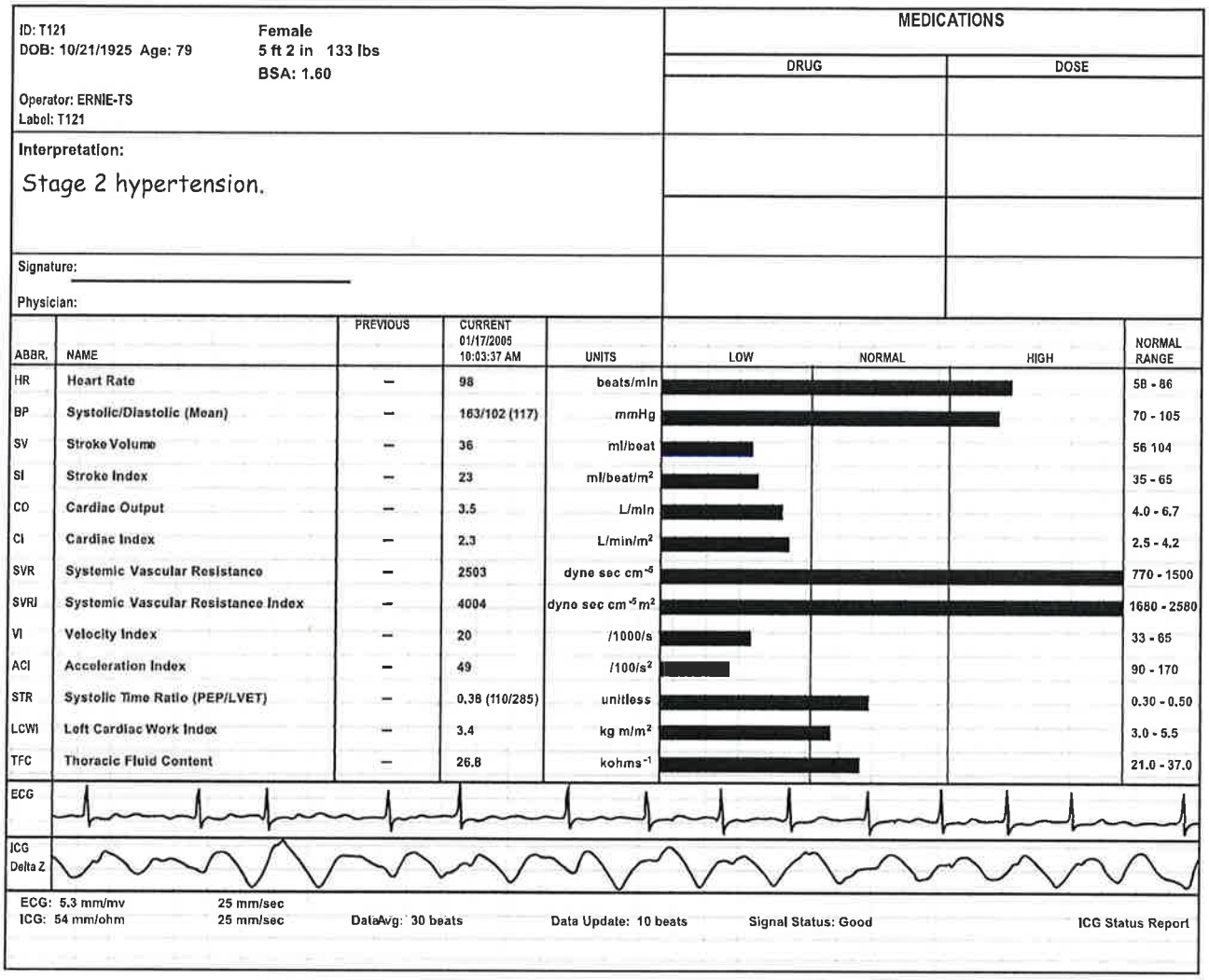


Figure 4. Impedance cardiography status report.

physicians to communicate with and educate patients on the underlying hemodynamic abnormalities causing their high BP, rationale for initial antihypertensive therapy, and subsequent changes to the pharmacologic regimen. Previous experience suggests that ICG hemodynamic-based patient education facilitates patient-physician communication, patient compliance to medication, and shared decision making between the physician and the patient. It has been reported that patient–physician communication is an integral part of clinical practice and patients who understand explanations from their physicians are more likely to acknowledge health problems, understand treatment options, modify behavior accordingly and follow medication schedules [Travaline *et al.* 2005; Bull *et al.* 2002; Ciechanowski *et al.* 2001; Bogardus *et al.* 1999; Stewart, 1995].

Access to underlying and ongoing hemodynamic causes of high BP with ICG may also reduce therapeutic inertia (TI) and suboptimal drug regimens. These two conditions cause inadequate pharmacologic treatment, which remains the most common cause of uncontrolled BP in actively treated patients [Yakovlevitch and Black, 1991]. TI, or failure of a clinician to begin new medications or increase dosages of existing medications when treatment goals are unmet, has a major impact on BP control in the US, and a significant decline in TI is necessary in order to reach the DHHS 'Healthy People 2010' goal of controlling BP to <140/90 mmHg in 70%

of all treated hypertensive patients by 2010 [Brookes, 2006; Okonofua *et al.* 2006]. Additionally, experts suggest that interventions which reduce TI have potential to significantly improve hypertension control rates [Okonofua *et al.* 2006].

Translation of research findings into improvements in clinical and patient outcomes remains a substantial obstacle to improving the quality of care [Agency for Healthcare Research and Quality, 2001]. The Smith *et al.* study [2006] was designed to test whether the results achieved in the Taler *et al.* [2002] Mayo clinic research academic study could be achieved in the routine clinical practice of nonspecialists treating nonresistant hypertensive patients. It is encouraging that similar results were obtained in both RCT settings [Smith *et al.* 2006; Taler *et al.* 2002], as well as the single-arm interventional trials [Aoka, 2009; Sramek *et al.* 2008, 1996]. It has also been reported that BP control rates are lower in clinical practice than contemporary clinical trials [Okonofua *et al.* 2006]. Notably is a very large, observational study in a clinical practice where BP control rates improved from 42% to 85%, after implementing ICG-guided therapy for patients not at goal BP [Matthews *et al.* 2008]. This study validates that implementation of ICG-guided therapy works in clinical practice, as seen over a period of years and tens of thousands of patient visits, and BP control rates achieved were actually higher than clinical trials.

BP remains uncontrolled most often because of persistent elevations in systolic BP [Calhoun *et al.* 2008]. Increases in systolic BP are a pathophysiologic concept accompanied by activation of the RAS, leading to large-artery stiffness [Duprez, 2008]. These effects manifest in elevated SVRI, whereby ICG-guided algorithms direct clinicians to a RAS blockade agent or direct vasodilator, thereby lowering the systolic BP. Secondary analysis of individual systolic and diastolic BP data from the Smith *et al.* study [2006] demonstrated 80% systolic BP control (<140 mmHg) in the ICG arm as compared to 60% in the standard care arm. This finding may have important implications in the treatment of systolic hypertension, a significant public health issue in the elderly. Systolic BP increases with age and is associated with increased CV morbidity and mortality. Since therapeutic goals are often not reached when treating systolic hypertension, it has been reported that there is a need for more effective, individualized antihypertensive therapy [Duprez, 2008], and this secondary analysis supports the effectiveness of individualized ICG-guided therapy in treatment of systolic hypertension.

Although significant improvements in awareness, treatment and control rates for hypertensive patients have occurred over the past 30 years, it has been argued that guidelines are not patient specific enough to be useful and do not allow for individualization of care, instead adopting one-size-fits-all thinking [Shaneyfelt and Centor, 2009]. This is not surprising as the BP lowering responses and benefits of a particular antihypertensive drug are not likely to be equal for all patients [Peverill, 2005; Mokwe *et al.* 2004; Sehgal, 2004], yet clinical study results are broadly applied to entire populations or population segments when incorporated into national committee guidelines. Physicians treat individuals, not populations. The optimal management of hypertensive patients should involve consideration of each patient's clinical conditions; underlying hemodynamic causes of the patient's hypertension; and pharmacology of antihypertensive medications. With these considerations, we can truly individualize the treatment of hypertensive patients.

Hypertension will cost the US healthcare system over $73 billion in 2009 [Stason, 2009], an increase from $69 billion in 2008. Health policy experts report that hypertension treatment is cost-effective and a very good use of healthcare resources [Stason and Weinstein, 1977; Weinstein and Stason, 1976]. Of note, is a study by Ferrario *et al.* [2006] evaluating the cost-effectiveness of ICG-guided hypertension therapy in usual clinical care using data from the previously described, 11-center RCT of family practice and internal medicine physicians in the CONTROL trial [Smith *et al.* 2006]. Costs incurred in both arms included office visits, prescribed medications, and in the ICG-guided arm only, the cost for ICG test performance was included. Short-term costs were calculated from baseline to study completion. The ICG arm had 44% lower costs for systolic BP ($20/mmHg for ICG *versus* $36/mmHg for standard care) and 71% lower costs for diastolic BP ($23/mm Hg for ICG *versus* $79/mmHg for standard care). Long-term costs were determined by standard methods. Long-term savings resulted in net cost savings for each year of quality

adjusted life years (QALY) gained. The authors concluded that ICG-guided therapy was both short- and long-term cost-effective [Ferrario *et al.* 2006]. The Smith *et al.* [2006] CONTROL ICG clinical study and associated CONTROL cost-effectiveness study [Ferrario *et al.* 2006] characterize a diverse and representative sample of usual primary care practices. Furthermore, these studies confirm both clinical and cost-effectiveness of ICG in usual primary care practices for the treatment of hypertension, as compared with standard care, which is the goal of comparative effectiveness research (CER) [New England Health Care Institute, 2009].

Given the results of this meta-analysis, the cost-effectiveness of ICG-guided hypertension treatment [Ferrario *et al.* 2006], and the recent $1.1 billion in US government stimulus funds for comparative effectiveness research (CER) [Connolly, 2009; States, 2007], which aims to find the best healthcare treatment at the lowest cost, ICG should be included in hypertension guidelines for uncontrolled hypertensive patients and receive enhanced coverage by third-party insurers.

Limitations of the study

The major limitation of this study is that we based the meta-analysis on only two RCTs as these were the only RCTs which were identified in our search. Further, these RCTs include fewer than 300 subjects, although they were prospectively powered for these patient numbers. It is well known that large differences in efficacy require much smaller patient numbers to show statistical power, of which both RCTs demonstrated. Fortunately, the results of the two studies are very similar and so support the hypothesis that ICG improves BP control to the findings, despite their relatively small sample sizes. It would have been preferable had the prospective single-arm interventional trials included a control arm, against which to compare the ICG-treated arm. Nonetheless, these interventional data are not considered key to the conclusions of this study and serve as supportive material to the two randomized trials.

Conclusions and future perspectives

The results of this meta-analysis confirm the value of using ICG-derived hemodynamic data as an adjunct to therapeutic decision-making in the treatment of hypertension. To further improve hypertension control rates and adherence to hypertension guidelines, experts have called for multiple strategies [Wang and Vasan, 2005] incorporating patient-individualized regimens [Stason, 2009; Calhoun *et al.* 2008; Duprez, 2008; Smith and Levy, 2008; Ferrario *et al.* 2007; Flack, 2006; Smith *et al.* 2006], evidence-based medicine [Jones, 2008], and practical, easy to apply, cost-effective principles [Jones, 2008; Ferrario *et al.* 2007]. ICG meets all these objectives; in randomized [Smith *et al.* 2006; Taler *et al.* 2002] and single-arm prospective trials [Aoka, 2009; Sramek *et al.* 2008, 1996], ICG allows tailoring specific antihypertensive drug regimens to patients' individual hemodynamic profiles to achieve target BP in an easy-to-apply, cost-effective manner [Ferrario *et al.* 2006]. Improving the success rate of BP control with ICG will likely reduce mortality and long-term adverse CV events associated with hypertension, as well as short- and long-term costs. ICG may meaningfully contribute to hypertension control and cost reduction as it is adopted by the medical community and insurers in a more expansive manner.

Conflict of interest statement

Carlos M Ferrario, MD receives compensation by consulting for CardioDynamics, Inc. and participating as a speaker for Novartis, Inc., Daiichi Sankyo, Inc., Merck, Inc., and Forest Pharma, Inc.

John Flack, MD is a consultant to Merck, Inc., Glaxo Smith-Kline, Bristol Myers Squibb, Novartis Inc., CVRx Inc., CardioDynamics Inc., and Myogen Inc. John E Strobeck, MD, PhD is a consultant for CardioDynamics Inc. Gerard Smits, PhD has served as a consultant for CardioDynamics Inc.

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